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Building Traceable Rheumatoid Arthritis Efficacy Endpoints with ADaM

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Abstract: ***Rheumatoid arthritis efficacy analyses combine joint counts, acute-phase reactants, patient and physician assessments, and functional-status questionnaires. Composite endpoints are difficult to validate when component-level derivations, visit selection, and analysis populations are not aligned. This paper describes an anonymized ADaM-oriented framework for deriving rheumatoid arthritis efficacy endpoints from observed and calculated components. It covers 66-joint swollen and 68-joint tender counts, C-reactive protein, pain and global assessments, the eight-domain Health Assessment Questionnaire Disability Index (HAQ-DI), ACR response criteria, disease activity indices, and analysis flags. It also explains how to keep on-treatment and all-available records distinct and how to represent nonresponder imputation and last-observation-carried-forward records without obscuring observed data. The examples reflect protocol-specific implementation conventions from historical presentation materials; they are not universal clinical recommendations. No patient-level results are reported. The main lesson is to derive and validate each component before calculating composites, with units, cutoffs, missing-data rules, and record-selection logic documented in the SAP and metadata.***

Keywords: rheumatoid arthritis, ACR response, HAQ-DI, ADaM, composite endpoints, imputation

1. Introduction

Rheumatoid arthritis (RA) efficacy endpoints integrate joint counts, acute-phase reactants, global assessments, pain, and functional status. Some endpoints use a single observed component; others combine components collected on different dates within an analysis window. A reliable analysis therefore needs clear rules for component derivation, visit-level selection, composite calculations, and population flags.

This paper develops an anonymized implementation framework from historical presentation materials. Sponsor, drug, protocol identifier, trial name, treatment assignments, sample size, branding, and identifying study details have been removed. No patient-level results are reported. The examples describe programming patterns, not universal endpoint recommendations. Current protocol, SAP, and applicable standards govern a production analysis.

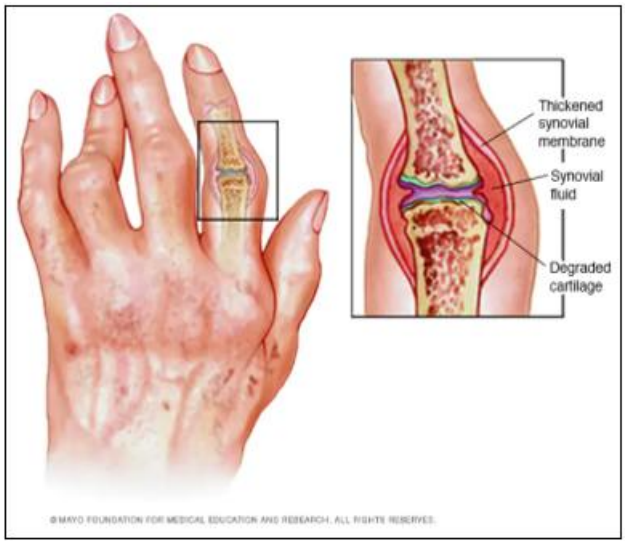


Figure 1

Component-Level Analysis Data

Begin with component datasets that preserve observed and calculated values separately. Common RA components include tender and swollen joint counts, C-reactive protein (CRP), patient pain, patient global assessment, physician global assessment, and HAQ-DI. A disease-specific CDISC therapeutic-area guide can provide metadata examples for representing these concepts consistently with foundational standards. CDISC standards describe structure and metadata; they do not prescribe the clinical measures to collect or endpoint definitions. [1, 2]

Component dataset	Example parameters	Critical derivation controls
Joint-count summary	Tender 68, swollen 66, tender 28, swollen 28	Evaluable-joint denominator and missingness rule
Acute-phase reactant	CRP	Unit, laboratory source, visit window, and record selection
Disease assessments	Pain, patient global, physician global	Scale range, direction, and respondent identity
Function summary	Eight HAQ-DI domains and total score	Question-to-domain mapping, aids and devices, missing domains
Composite endpoint	ACR response, CDAI, SDAI, DAS28-CRP	Component visit alignment, formula, unit, and response cutoff

For joint counts, the data specification should define whether a visit is evaluable when fewer than the full set of joints is assessed. One implementation example treats a count as missing if fewer than half of the required joints are evaluated. That rule is study-specific. The component record should retain the assessed-joint count so reviewers can verify the evaluability decision.

Therapeutic Area User Guide (TAUG) RA v1.0

TAUG provides information on ADaM names, structure and CTs.

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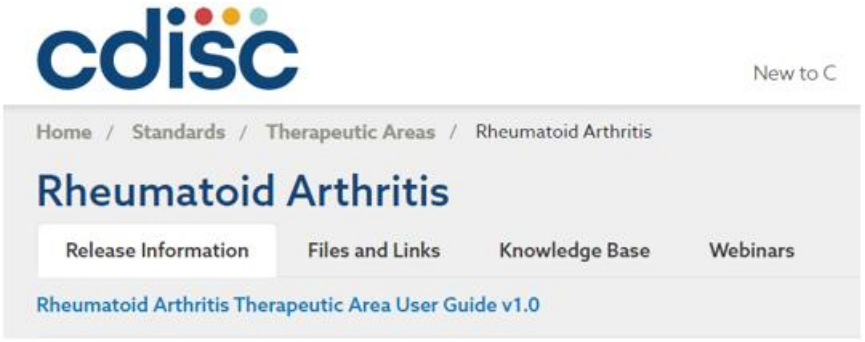
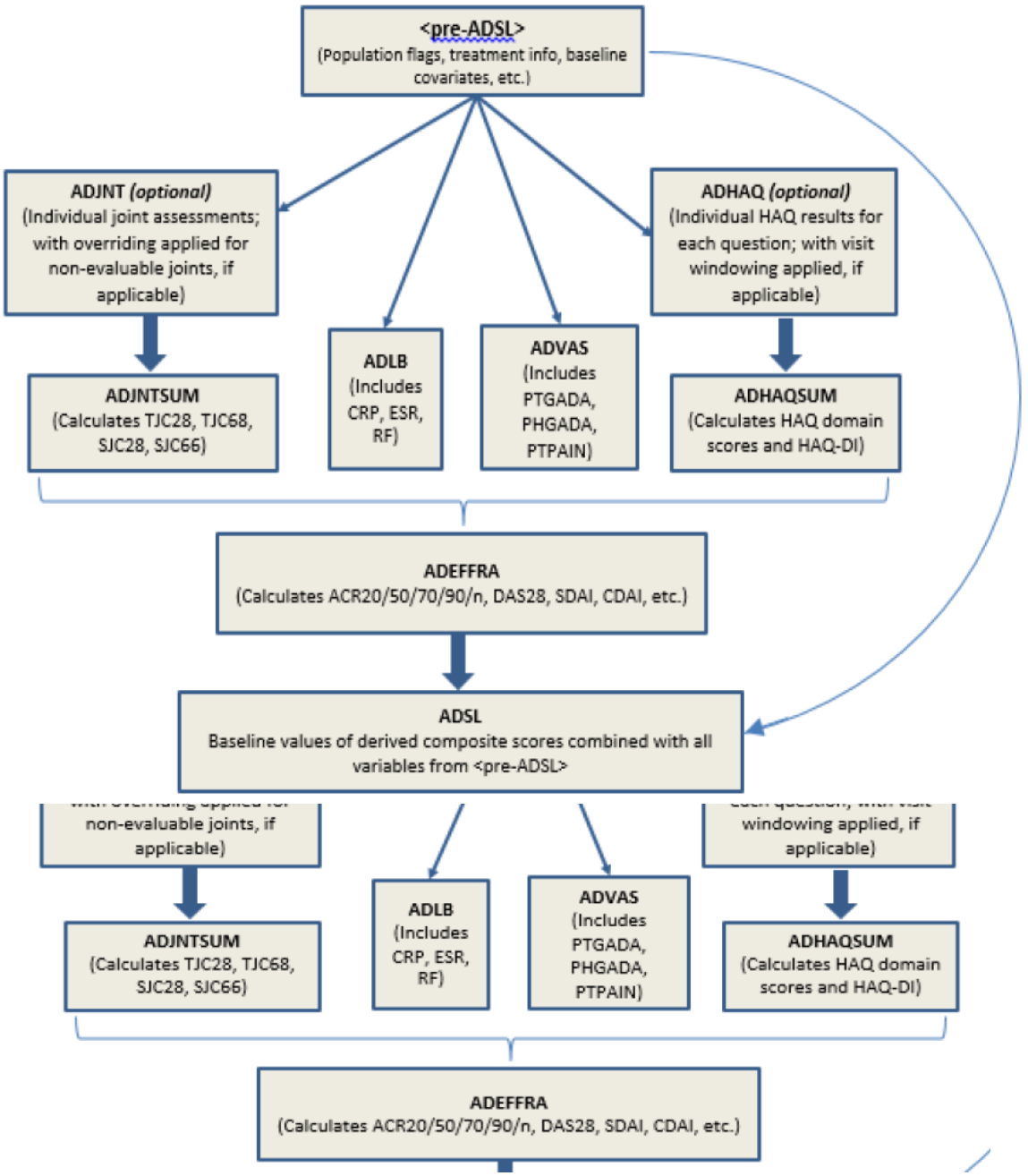


Figure 2: Analysis Dataset Flow



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DAS28CRP (Disease Activity Score for 28 Joint Count using CRP):

$$DAS28(CRP) = 0.56\sqrt{TJC28} + 0.28\sqrt{SJC28} + 0.36\ln(CRP + 1) + 0.014 \times SGA + 0.96$$

– Units: CRP (mg/L); SGA (mm)

SDAI (Simplified Disease Activity Index) = TJC28+SJC28+SGA+PGA+CRP

CDAI (Clinical Disease Activity Index) = TJC28+SJC28+SGA+PGA

– Units: CRP (mg/dL); SGA (cm); PGA (cm)

ADJNTSUM (Joint Counts)	ADCRP (CRP)	ADVAS (Disease Assessments)	ADEFFRA (Composite Endpoints)
TJC28	CRP	PTGADA	DAS28CRP
SJC28		PHGADA	CDAI
			SDAI

HAQ-DI Scoring

The HAQ-DI measures difficulty across eight functional domains: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and usual activities. Items are scored on a 0-to-3 scale, and the domain score generally reflects the highest item score in that domain. Use of an aid or device can raise a domain score to at least 2, according to the instrument and protocol rules. The total score is the mean of the domain scores, not a simple sum of all questionnaire responses. [3]

A robust derivation maps each questionnaire item to its domain and retains the item-level responses, domain score, and adjustment reason. If one or two domain scores are missing, an example rule calculates the mean of the available domains; if more than two domains are missing, it sets the total to missing. This is a protocol-specific completeness convention and should be verified against the licensed instrument, its scoring manual, and the SAP. A minimal clinically important change threshold should be treated as a separately specified binary endpoint, with the qualifying baseline range explicitly stated.

$$TJC68 = \frac{Total\ number\ of\ tender\ joints}{68 - (Number\ of\ nonevaluable\ or\ missing\ joints\ out\ of\ 68\ joints)} \times 68$$

TJC68: 68 Tender Joint Count (TJC68): all joints marked by circles on the picture are assessed for tenderness (Some joints might be non-evaluable or missing).

ADHAQSUM - Questionnaire

HAQ-DI (the Health Assessment Questionnaire Disability Index) - combined direct measurements collected at a single timepoint.

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HAQ-DI Category:	Category questions: At least 6 categories must have scores to compute the HAQ-DI.	
	Category Questions	Aids/Devices Indicators
Dressing / Grooming	HAQ0101, HAQ0102 (DRESS, HAIR)	HAQ0114, HAQ0119 (DRSG, GROOM)
Arising	HAQ0103, HAQ0104 (STAND, BED)	HAQ0116, HAQ0120 (CHAIR, ARISING)
Eating	HAQ0105,HAQ0106, HAQ0107 (MEAT, LIFT,MILK)	HAQ0115, HAQ0121 (UTENSIL, EAT)
Walking	HAQ0108, HAQ0109 (WALK, STEPS)	HAQ0110, HAQ0111, HAQ0112, HAQ0113, HAQ0122 (CANE, WALKER, CRUTCH, WHEEL, WALKING)
Hygiene	HAQ0123, HAQ0124, HAQ0125 (WASH, BATH, TOILET)	HAQ0134, HAQ0135, HAQ0137, HAQ0139, HAQ0142 (RAISEAT, BATHBAR, BATHSEAT, LONGBATH, HYGIENE)
Reach	HAQ0126, HAQ0127 (REACH, BEND)	HAQ0138, HAQ0143 (LONGRCH, REACH)
Grip	HAQ0128, HAQ0129, HAQ0130 (OPENCAR, JAR, FAUCET)	HAQ0136, HAQ0144 (JAROPEN, GRIP)
Activity	HAQ0131, HAQ0132, HAQ0133 (SHOP, INCAR, CHORES)	HAQ0145 (ERRAND)

ADHAQSUM – Domain Score

Domain score calculation: max(XX category questions, 2*aids indicator)

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Composite Endpoints

ACR20, ACR50, and ACR70 classify improvement using the same percentage threshold in both tender and swollen joint counts and in at least three of five additional core measures: patient global assessment, physician global assessment, pain, physical disability, and an acute-phase reactant. The ACR definition was developed from a core set of RA trial outcome measures. [4] The dataset should preserve the percent change in every component and the resulting criterion flags before generating the composite response.

ACR-N is a continuous measure of improvement based on joint-count changes and the median improvement across the other core components. Its exact handling of negative changes, missing components, and baseline zeros must follow the prespecified algorithm. A Boolean remission endpoint is a separate construct and should not be inferred from ACR response.

CDAI, SDAI, DAS28-CRP, and EULAR response criteria each use a different formula or decision structure. CDAI combines 28-joint counts and patient and physician global

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assessments. SDAI adds CRP. DAS28-CRP uses a specified calculation and unit convention. EULAR response categories consider both current disease activity and change from baseline. Cutoffs should be tied to the exact version and scale used; do not mix a CRP value reported in mg/L with a formula that expects mg/dL or mix global-assessment scales. The 2011 ACR/EULAR provisional remission definition provides one trial framework; a historical endpoint should be labeled as defined in that study rather than presented as the current standard. [5]

Endpoint family	Inputs to align	Output form
ACR response	TJC68, SJC66, five core measures	Binary response at prespecified 20%, 50%, or 70% threshold
Disease activity index	28-joint counts and global assessments; CRP for indices that include it	Continuous score and optionally disease-activity category
EULAR response	DAS28 value at visit and change from baseline	Good, moderate, or no response category
Function improvement	HAQ-DI baseline and post-baseline value	Change and separately specified responder flag

Component Visit Selection and Analysis Flags

Composite endpoints should be derived only after each component has been assigned to its analysis visit. If the component assessments occur on different calendar dates, the SAP should define window limits, tie-breakers, and whether the nearest, latest, or otherwise prioritized record is selected. The composite dataset typically links components by subject, analysis visit, and parameter, not by assuming all values share one collection date.

Separate analysis flags can represent distinct analysis populations. An all-available analysis may include post-rescue or post-treatment data, while an on-treatment analysis may exclude records outside a prespecified exposure window. If a trial changes treatment after a disease-response rule, the date and population definition need explicit treatment. The two flags are not necessarily nested: independent record-selection rules can select different visits within the same analysis window. Apply flags consistently to component datasets before deriving the composite, then verify that the final endpoint inherits the intended component records.

Missing-Data Records and Imputation

Imputation records should be distinguishable from observed records through derivation-type metadata. Binary endpoint NRI may classify a missing response as nonresponse at the target visit. LOCF may carry a prior observed continuous component forward when permitted by the SAP. If a binary classification depends on a continuous component, the continuous LOCF record and binary NRI record may both be needed, but they answer different analysis questions. They must not be collapsed into one value or selected together accidentally.

For example, when the target visit lacks a required joint count, an NRI record can represent the response endpoint as nonresponse. A separate LOCF record may be created for an approved sensitivity analysis using the prior joint count. Each record should carry the visit, source visit, derivation type, baseline value, change, criterion flag, and analysis flag. Before implementation, define precedence where multiple derived records exist and test how they interact with visit windows and treatment discontinuation.

Validation and Reporting

Unit tests should cover component bounds, partial joint counts, missing questionnaire items, aid-use adjustments, missing domains, unit conversions, cutoff equality, negative changes, baseline-zero values, conflicting component dates, and treatment-rescue boundaries. Independent validation should recompute scores from raw or standardized source records and compare intermediate components as well as final endpoints. Listings for unusual or imputed records help identify unexpected patterns.

A concise derivation specification should map each endpoint to its component datasets, parameter codes, units, visit-selection rule, baseline type, formula, missing-data method, analysis flag, and output use. The SAP and metadata should be aligned before table programming begins. That alignment reduces the chance that the same component is defined differently in a primary analysis, sensitivity analysis, and data review listing.

2. Conclusion

Traceable RA efficacy programming starts with accurate component-level analysis datasets. Questionnaire scoring, joint-count evaluability, unit conventions, visit alignment, and analysis-population flags all affect composite endpoints. Explicitly preserving observed and derived records makes the final ACR responses and disease activity measures easier to reproduce and review. Reconcile every example with the study's protocol, SAP, instrument requirements, and current CDISC and clinical guidance before submission or reuse.

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